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ORIGINAL ARTICLE

Alterations of bone microstructure and strength in end-stage renal failure

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Abstract
Summary End-stage renal disease (ESRD) patients have a high risk of fractures. We evaluated bone microstructure and finite-element analysis-estimated strength and stiffness in patients with ESRD by high-resolution peripheral computed tomography. We observed an alteration of cortical and trabecular bone microstructure and of bone strength and stiffness in ESRD patients.
Introduction Fragility fractures are common in ESRD patients on dialysis. Alterations of bone microstructure contribute to skeletal fragility, independently of areal bone mineral density.
Methods We compared microstructure and finite-element analysis estimates of strength and stiffness by high-resolution peripheral quantitative computed tomography (HR-pQCT) in 33 ESRD patients on dialysis (17 females and 16 males; mean age, 47.0±12.6 years) and 33 age-matched healthy controls.
Results Dialyzed women had lower radius and tibia cortical density with higher radius cortical porosity and lower tibia cortical thickness, compared to controls. Radius trabecular number was lower with higher heterogeneity of the trabecular network. Male patients displayed only a lower radius cortical density. Radius and tibia cortical thickness correlated negatively with bone-specific alkaline phosphatase (BALP). Microstructure did not correlate with parathyroid hormone (PTH) levels. Cortical porosity correlated positively with "Kidney Disease: Improving Global Outcomes" working group PTH level categories ($r=0.36$, $p<0.04$). BMI correlated positively with trabecular number ($r=0.4$, $p<0.02$) and negatively with trabecular spacing ($r=-0.37$, $p<0.03$) and trabecular network heterogeneity ($r=-0.4$, $p<0.02$). Biomechanics positively correlated with BMI and negatively with BALP.
Conclusion Cortical and trabecular bone microstructure and calculated bone strength are altered in ESRD patients, predominantly in women. Bone microstructure and biomechanical assessment by HR-pQCT may be of major clinical relevance in the evaluation of bone fragility in ESRD patients.

Keywords Bone microarchitecture · Chronic kidney disease · Dialysis · High-resolution peripheral quantitative computed tomography

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Introduction

Chronic kidney disease (CKD) affects 10 % of the population and is associated with alterations in bone and mineral metabolism. In up to 75–100 % of patients, bone disease occurs when the glomerular filtration rate (GFR) falls below 60 ml/min per 1.73 m^2 and is commonly referred to as renal osteodystrophy or, more recently, chronic kidney disease–mineral bone disease (CKD–MBD) [1, 2]. Several types of disorders can be observed, ranging from high-turnover (hyperparathyroidism) to low-turnover bone lesions (adynamic bone). In addition to renal failure, CKD–MBD may be worsened from a combination of various factors such as vitamin D deficiency, hyperparathyroidism, malnutrition, the use of certain drugs (corticosteroids, phosphate binders, vitamin D analogs), or hypogonadism [3]. It is associated

also with increased morbidity (vascular lesions, fractures, cardiovascular events) and higher mortality [4, 5].

Compared to a normal population, fracture occurrence is higher in CKD patients at all skeletal sites, e.g., hip, vertebral, wrist, as soon as GFR falls below 60 ml/min per 1.73 m^2 [6, 7]. In dialyzed patients (end-stage renal disease, ESRD), there is a fourfold increased risk of hip fracture [8] that positively correlates with age, duration of dialysis, low parathyroid hormone (PTH) levels [9], female gender, low body mass index (BMI), presence of peripheral vascular disease, and tobacco abuse [8].

Histomorphometric analysis of bone biopsy specimens after double tetracycline labeling assesses bone microstructure and turnover, but is limited by the invasiveness of the procedure [10]. Dual X-ray absorptiometry (DXA) measures areal bone mineral density (aBMD), which is a predictor of fracture risk in osteoporosis and CKD–MBD [11]. However, DXA is unable to analyze bone microstructure, cannot easily differentiate between cortical and trabecular bone, and is influenced by artefactual vascular calcification projections, particularly at the lumbar spine level. Microstructure alterations contribute to bone fragility, irrespective of aBMD [12, 13].

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a noninvasive procedure that discriminates between trabecular and cortical bone and quantitatively evaluates microstructure variables, including cortical porosity (CtPo), with a 82-μm-voxel resolution. CT datasets from individual scans can be used for microstructural finite-element analysis (FEA) to assess bone mechanical competence (failure load and stiffness). Few studies have evaluated hemodialysis patients with these techniques [14, 15], but they indicate an alteration of both cortical and trabecular bone compartments in relation to the severity of secondary hyperparathyroidism. The aim of this study was to analyze bone 3D microstructure, CtPo, and biomechanical properties in both compression (FEA) and torsion (polar moment of inertia) by HR-pQCT in ESRD patients compared to age-, gender-, and weight-matched healthy controls.

Patients and methods

Subjects

Subjects consisted of 33 individuals on chronic dialysis (16 men and 17 women, 9 postmenopausal and 8 premenopausal; median age, 50.4 (interquartile range, 16.7 years)) recruited at the Geneva University Hospitals, Geneva, Switzerland. Inclusion criteria were >18 years and hemodialysis (n=26) or peritoneal dialysis (n=7) for more than 3 months. Exclusion criteria were previous treatment with bisphosphonates, other metabolic diseases with an impact on bone (e.g., Paget disease, osteogenesis imperfecta), pregnancy, or previous renal transplant with a graft survival of more than 3 months. Patients were hemodialyzed three times a week during 4 h using a dialysate calcium concentration of 1.5 mmol/l. The dialysate calcium concentration of patients on peritoneal dialysis was 1.25 mmol/l.

Patients were categorized according to the PTH level defined in the Kidney Disease: Improving Clinical Outcomes (KDIGO) recommendations [16]: low bone turnover for intact PTH levels lower than 13.6 pmol/l (twice the upper normal limit of the assay), normal bone turnover for intact PTH levels between 13.6 and 61.2 pmol/l (nine times the upper normal limit), and high bone turnover for intact PTH above 61.2 pmol/l, based on a mean PTH value of two samples measured at 3-month intervals.

Patients were compared to 33 age-, gender-, and weight-matched healthy controls. Women were also matched according to their menopausal status. Controls were recruited mainly among the hospital staff and their families, per personal contact and advertisement. To compute the patient T-score, we studied also 83 young healthy individuals (58 females and 25 males; mean age, 22.7±3.8 years) recruited during the same period, i.e., a population at peak bone mass. The protocol was approved by the ethics committee of Geneva University Hospitals, and written informed consent was obtained from each patient and healthy subject.

Clinical assessment

Height was determined by a Holtain stadiometer (Holtain, Crosswell, Wales). Weight was determined on a calibrated scale to the nearest 0.1 kg. BMI was calculated from weight-to-height ratio (in kilogram/height in meters squared). Calcium and protein intakes were recorded by a validated food frequency questionnaire [17]. Family history of fracture, tobacco use, alcohol intake, medical history, presence and type of atraumatic fracture, and presence, type, indication, and dose of prior treatment potentially influencing bone metabolism were determined in all subjects. The age at last menses defined menopausal age and was determined in all postmenopausal women; menopause was of physiological origin in all patients. Time since first dialysis at inclusion was computed. Nutritional status was determined using the mini-nutritional assessment short form (MNA-SF) [18], which includes six items (appetite, weight loss, mobility, acute disease or psychological stress, cognitive dysfunction or depression, and BMI). Dialysis parameters Kt/V (fractional urea clearance controlled for volume of distribution) and percent reduction of urea (PRU) were used to evaluate the efficacy of dialysis [19]. Frequency and time of dialysis [20], as well as calcium and bicarbonate dialysate concentrations, were recorded.

Areal BMD assessment

aBMD at the level of the lumbar spine (LS) in antero-posterior view, femoral neck, and total hip was measured by DXA using a Hologic QDR 4500 instrument (Hologic, Inc., Waltham, MA, USA). The coefficient of variation of repeated BMD measurements was 1–2 % [21, 22]. BMD (in gram per square centimeter) was also expressed as a T-score, which compares individual BMD values with those of a young normal population of the same gender (number of standard deviations from the mean) [23], using the 3rd National Health and Nutrition Examination Survey or HOLOGIC database [23]. Vertebral fracture prevalence was evaluated by DXA-based vertebral fracture assessment [24].

High-resolution peripheral quantitative computed tomography assessment

Volumetric bone density and cortical and trabecular microstructure were determined at the nondominant distal radius in 28 of 33 (21 of 26, hemodialysis; 7 of 7, peritoneal dialysis) patients using a HR-pQCT instrument (XtremeCT, Scanco Medical AG, Bruettisellen, Switzerland) as previously described [12, 25]. The dominant arm was measured in five patients, given the presence of arterio-venous fistula on the nondominant one. Tibia data were obtained on ipsilateral tibia except for patients with dominant radius data. The system uses a 2D detector array in combination with a 0.08-mm point-focus X-ray tube, enabling the simultaneous acquisition of a stack of parallel slices with a nominal resolution (voxel size) of 82 μm. The following settings were used: effective tension of 60 kVp, X-ray tube current of 900 μA, and matrix size of 1,536×1,536. At each acquisition site, 110 slices were obtained, leading to a 3D representation of approximately 9 mm in the axial direction. All examinations were analyzed by the same observer. The radiation effective dose was 3 μSv per measurement with an acquisition time of 3 min. The reproducibility of HR-pQCT at the distal tibia was assessed in 15 healthy subjects (with repositioning) and varied from 0.7 to 1.0 % and from 3.0 to 4.9 % for bone density and for trabecular architecture, respectively [26]. These reproducibility data ranges are similar to those previously published with the same device [12]. The reproducibility of the FE-calculated stiffness and strength was better than 3.3 % and is very similar to values reported for the reproducibility of morphological measures of the same data set (Bert Van Rietbergen et al., personal communication).

The following variables were recorded [25]: total (Dtot), cortical (Dcort), and trabecular (Dtrab) volumetric density, expressed as milligram hydroxyapatite-equivalent per cubic centimeter; relative trabecular bone volume fraction (BV/TV, in percent); trabecular number (TbN); trabecular thickness (TbTh, in micrometer); trabecular separation (TbSp, in micrometer); heterogeneity of the trabecular network (TbSp.SD); cross-sectional area (CSAtotal, in square millimeter); cortical thickness (CTh, in millimeter), and CtPo (in percent) [27]. CtPo was quantified using customized analysis tools [27–29] and calculated as the number of void voxels within the cortex. BV/TV is derived from Dtrab assuming that fully mineralized bone has a mineral density of 1,200 mg HA/cm^3. TbN was defined as the inverse of the mean spacing of the mid-axes. TbTh and TbSp were derived from BV/TV and TbN using standard histomorphometric methods. TbSp.SD was evaluated by measuring the standard deviation of the individual distribution of the TbSp. The system provides a direct assessment of cortical bone density. CTh is defined as the mean cortical volume divided by the outer bone surface.

High-resolution peripheral quantitative computed tomography image-based biomechanical analysis

FEA of HR-pQCT scans was used to calculate biomechanical properties relevant for compression. We generated finite-element models directly from the 3D HR-pQCT image data using the voxel-conversion approach [30–32]. Outcomes included stiffness (in newton per millimeter), calculated as the reaction force (RFz) determined by the FEA divided by the applied displacement, and estimated failure load (in newton) using the Pistoia criterion [32]. We determined also the percentage of the total load that is carried by trabecular bone at the most distal slice and the apparent modulus, which was defined as the reaction force divided by the projected cross-sectional area and the applied longitudinal strain [33].

To quantify the stiffness of the bone for torsion loading, the polar moment of inertia was calculated using the manufacturer's software.

Biochemical data

Plasma calcium, phosphate, total CO_2, and creatinine were measured with an automatic analyzer (Beckman Coulter DxC800; Beckman Coulter, Inc, Orange County, CA, USA). Plasma calcium was adjusted for albumin levels (adjusted Ca= Ca+[0.02×(40-albumin)]). Serum PTH and osteocalcin were measured using a two-site chemiluminescent immunometric assay (Elecsys R, Roche, Basel, Switzerland). Bone-specific alkaline phosphatase (BALP) was measured by enzyme immunoassay (Beckman Coulter I800). Insulin growth factor I (IGF-I) was measured by enzyme-labeled chemiluminescent immunometric assay (Siemens Immulite 2500; Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA).

Statistics

Results are presented as the means ± standard deviation. When the clinical and biological data were not normally

distributed, descriptive statistics are given as the median and 95 % confidence interval (CI). Normality was verified by using Shapiro–Francia tests. Comparisons between ESRD patients and age-matched controls for continuous variables were performed with a Wilcoxon matched-pairs signed-ranks test to take into account the matched design. Comparisons between ESRD patients and young healthy controls were performed with a Kruskal–Wallis equality-of-populations rank test. Chi-squared tests were used for comparing proportions.

Correlations between HR-pQCT parameters and variables were determined by Spearman rank correlation for non-normally distributed variables. The significance level for two-sided p values was 0.05 in all tests. All statistical analyses were performed using STATA software (version 11.0; Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

The 33 patients with ESRD (16 men and 17 women, nine of them being postmenopausal) were 47.0±12.6 years old. Median time of dialysis was 0.95 years (95 % CI, 0.75–2.30 years). Table 1 reports the leading causes of renal failure. No patient had a family history of fragility fracture. Five patients (15 %) reported a history of low-trauma clinical fracture (four females and one male); four occurred before initiation of dialysis (three females and one male), and all were non-vertebral. Dialysis patients and control subjects did not differ in age, weight, or BMI, but patients were 2±5 % shorter compared to matched controls (Table 1). According to the KDIGO recommendations for PTH levels in ESRD patients [16], 25 patients were in the targeted values (PTH between 13.6 and 61.2 mmol/l), four had low PTH values (PTH under 13.6 mmol/l), and four had elevated values (PTH superior to 61.2 mmol/l) (Table 1).

Regarding concomitant medications affecting bone metabolism (Table 1), among patients receiving at least one medication, 13 (39 %) were treated with only a phosphate binder (calcium acetate or carbonate and/or sevelamer) and 2 with calcitriol as unique medication. Eight received a combination of a phosphate binder and calcitriol. Three patients were treated with the association of a phosphate binder and cinacalcet. Finally, two received a binder with cinacalcet and calcitriol in combination.

Areal BMD comparisons between patients, matched control, and young healthy population

Compared with young healthy individuals and matched controls, ESRD women had lower lumbar spine and hip aBMD (Table 2). In men, lumbar spine aBMD was significantly higher compared with matched controls. Hip aBMD was no different from control values. Prevalence of osteopenia and osteoporosis at any site was 52 % (17 of 33) and 15 % (5 of 33) in ESRD patients, and 48 % (16 and 33) and 6 % (2 and 33) in age-matched controls, respectively (not significantly different). Eleven patients (33 %) and 15 (58 %) controls had normal DXA values. Femoral neck BMD T-score in patients with fracture tended to be lower than in those observed without fracture, but this difference did not reach statistical significance (−1.8±1.0 in those with a fracture vs −1.2±1.1 in unfractured patients, p=0.17). Vertebral fracture assessment identified three silent vertebral fractures in patients without a clinical history of clinical fracture. Vertebral body height reduction was between 20 and 25 % in two patients and between 25 and 40 % in one patient.

Comparisons of vBMD and microstructural parameters between patients and controls

ESRD women had lower total and cortical densities at both sites compared with age-matched controls (−12 and −7 % for both distal radius and tibia, respectively, p<0.01; Table 3). Lower cortical density was associated with a higher porosity at the radius level (+82 %; p<0.05) and a lower CTh at the tibia (−12 %; p<0.05; Table 3). In women, there were also alterations of the trabecular compartment with a lower TbN (−12 %; p<0.05) and a higher heterogeneity of the TbSp.SD at the radius (+43 %; p<0.05). At the tibia, trabecular density was 11 % lower (p<0.05). Compared with young healthy controls, both distal radius and distal tibia cortical and trabecular compartment variables were lower (Table 3). In contrast to the DXA findings, male ESRD patients displayed a 7 % lower radius cortical density (p<0.01; Table 4). Compared with young male healthy controls, lower values in cortical density and thickness and in trabecular variables were mostly detected at the distal tibia and not at the distal radius.

FEA and polar moment of inertia

As determined by FEA, stiffness and predicted failure load at both distal radius and tibia were lower in ESRD women, but not in men, compared with age-matched controls (Table 5).

Relationship of aBMD, bone microstructural parameters, cortical porosity, and bone strength with demographic, dialysis, nutritional, and biological parameters

Using Spearman rank correlation analysis, we examined the relationship between aBMD, microstructural bone

Table 1 Characteristics of the subjects

	ESRD patients	Matched controls	Young controls
Number	33	33	83
Gender (M/F)	16/17	16/17	25/58
Number of menopausal women	9	9	0
Age (years)	47±13	48±13	23±4
Age of men (years)	48±12	51±14	27±4
Age of women (years)	46±13	46±12	21±2
Weight (kg)	71±18	68±12	63±12
Height (cm)	166±11*	169±9	169±9
BMI (kg/m^2)	25±5	24±3	22±3
Main causes of renal failure, *n* (%)			
Chronic glomerulonephritis	8 (24)		
Polycystic kidney disease	1 (3)		
Vascular disease[a]	14 (42)		
Tubular and interstitial diseases	1 (3)		
Diabetes	5 (15)		
Congenital renal anomalies[b]	1 (3)		
Other or unknown	6 (18)		
MNA-SF ($n \geq 12/14$) (median, 95 % CI)	12 [11-13]		
Concomitant medications affecting bone			
No treatment, *n* (%)	6 (18)		
Phosphate binders, *n* (%)	25 (76)		
Calcitriol, *n* (%)	11 (33)		
Cinacalcet, *n* (%)	5 (15)		
Protein intake (g daily)	61±22		
Protein intake per kg (g/kg daily)	0.9±0.3		
Calcium intake (mg daily, median, 95 % CI)	614 [564–725]		
Peritoneal dialysis (*n*)	7		
Kt/V[c]	1.6±0.3		
PRU (%, median, 95 % CI)	75 [71–79]		
Time on dialysis (years) (median, 95 % CI)	0.9 [0.8–2.3]		
Creatinine [N, 35–106 μmol/l]	843±291		
Albumin corrected calcium [N, 2.25–2.60 mmol/l]	2.30±0.17		
Serum phosphate [N, 0.80–1.4 mmol/l]	1.73±0.48		
Total plasma CO_2 [N, 23–30 mmol/l]	22.9±3.1		
Serum PTH [N, 1.1–6.8 pmol/l]	40±31		
Serum IGF-I [N, 116–447 ng/ml]	200±80		
Serum osteocalcin (median, 95%CI; N, 8.8–29.7 μg/l)	281 [95 % CI 147–329]		
Bone-specific alkaline phosphatase (median, 95 % CI) [N, 2.9–22.6 mmol/l]	16 [95 % CI 13–24]		

Results are means ± standard deviation for Gaussian continuous variables

N Normal range, *MNA-SF* mini-nutritional assessment short form, *PRU* percent reduction of urea

*$p<0.05$: dialyzed patients compared with matched controls

[a]Vascular disease includes vasculitis, thromboembolic disease, hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura, hypertension, scleroderma, unilateral or bilateral renal artery stenosis, and cholesterol atheroembolic disease

[b]Congenital renal anomalies includes aplasia, hypoplasia, and dysplasia. Patients may have multiple causes

[c]Fractional urea clearance controlled for volume of distribution for hemodialyzed patients

parameters, bone strength and time on dialysis, nutritional parameters (MNA-SF, daily calcium and protein intake, and plasma IGF-I used as a reflection of nutritional status), biological parameters including PTH, and bone formation markers (BALP, osteocalcin) (Table 6). Lumbar spine and total hip BMD positively correlated with BMI and MNA-SF, while lumbar spine BMD correlated negatively with BALP ($p<0.003$).

Distal radius cortical volumetric density and CTh correlated negatively with BALP. Distal radius cortical volumetric density was positively associated with MNA-SF. Radius CtPo was positively associated with KDIGO PTH level categories ($r=0.36$; $p<0.03$) (data not shown). There was no association between radius bone microstructural parameters and other dialysis or biological parameters. The percentage of load carried by trabecular bone at the distal radius

Table 2 Areal BMD in patients, matched controls, and young healthy individuals

	ESRD patients		Matched controls		Young controls	
	BMD (g/cm^2)	T-score (SD)	BMD (g/cm^2)	T-score (SD)	BMD (g/cm^2)	T-score (SD)
Women						
Spine	0.92±0.1*,**	−1.1 (1.0)	1.02±0.1	−0.1 (1.0)	1.03±0.1	−0.1 (1.2)
Femoral neck	0.65±0.1*,**	−1.8 (1.2)	0.75±0.1	−0.9 (0.8)	0.84±0.1	−0.1 (1.1)
Total hip	0.78±0.2*,**	−1.3 (1.3)	0.86±0.1	−0.6 (0.7)	0.93±0.1	−0.1 (1.1)
Men						
Spine	1.09±0.1*	−0.1 (0.8)	0.96±0.1	−1.2 (1.1)	1.02±0.1	−0.7 (0.9)
Femoral neck	0.83±0.1	−0.7 (0.9)	0.81±0.1	−0.9 (1.0)	0.91±0.1	−0.1 (1.0)
Total hip	0.98±0.1	−0.4 (0.8)	0.99±0.1	−0.3 (0.9)	1.04±0.12	0.0 (0.8)

SD standard deviation

$^{*}p<0.05$ as compared with age-, weight-, and gender-matched controls; $^{**}p<0.01$ as compared with young healthy controls

increased with the BALP serum level ($r=0.36$; $p=0.05$) and was negatively associated with the MNA-SF score ($r=-0.41$; $p=0.02$) (data not shown).

Distal tibia cortical thickness was negatively associated with BALP ($r=-0.37$; $p=0.04$). A positive association was observed between cortical volumetric density and MNA-SF ($p=0.02$). TbN correlated positively with BMI ($p<0.02$), while TbSp ($p<0.03$) and the TbSp.SD ($p<0.02$) correlated negatively with BMI. There was no association between tibia bone microstructural parameters and dialysis, nutritional status, and other biological parameters. At the distal tibia, a negative association with BALP was observed for stiffness ($r=-0.40$; $p=0.03$), predicted failure load ($r=-0.40$; $p=0.03$), and the cortical polar area moment of inertia ($r=-0.46$; $p<0.01$). Stiffness and predicted failure load were positively associated with BMI ($p<0.05$).

In order to delineate the structural effects and the resulting consequences on bone strength of a presumably low-turnover bone disease, we categorized the patients into two groups according to PTH levels: lower than 13.6 pmol/l which is the lower threshold for PTH values according to the KDIGO recommendations (two times the upper limit of normal values) and higher. Only four patients had such low PTH values. We compared the two populations and found that the group with the lower PTH level had a lower cortical porosity at the radius level ($p<0.03$).

Relationship of aBMD and bone microstructural parameters

We wanted to study whether and to what extent aBMD correlated with bone microstructural parameters assessed by HR-pQCT. We limit our analysis to variables directly measured and not derived from calculation. Areal BMD at LS and total hip were correlated with trabecular density ($r=0.44$ to 0.56, $p<0.05$) at either the radius or the tibia. Cortical density was not correlated to aBMD at any site. The cross-sectional area was highly correlated at the LS and total hip levels with r values ranging from 046 to 0.53 ($p<0.05$).

Discussion

The present study shows that the use of HR-pQCT to evaluate bone microstructure, CtPo, and estimates of bone strength and stiffness by FEA allows to detect alterations in densitometric and microstructural variables that may contribute to an increased fracture risk in ESRD patients beyond those identified by DXA-determined aBMD. The main findings are: (1) In ESRD women who seem to be more affected than men, there is a marked increase in the heterogeneity of the trabecular network and of cortical porosity, particularly at the distal radius level, and a lower distal tibia cortical thickness. (2) The decrease of bone density and microstructural alterations found in ESRD women are associated with lower calculated bone strength and stiffness at both skeletal sites. (3) Although dialyzed male patients have lower cortical and trabecular variables predominantly at the tibia compared to the young healthy population, only a lower radius cortical density was statistically significant when compared to age-matched controls with similar aBMD values. (4) Among the recorded factors, nutritional and anthropometric variables, as well as bone turnover, determine the differences in cortical and trabecular microstructural parameters and in bone strength and stiffness in ESRD patients. Cortical porosity is related to KDIGO categories of PTH levels.

To assess bone structural characteristics, several studies with pQCT have been conducted in patients with CKD or ESRD. The first studies used instruments with a 350-μm resolution and showed a lower cortical vBMD, but no significant differences in trabecular BMD in ESRD patients [34–36] compared with healthy controls. A recent cross-sectional study in 52 adults on maintenance hemodialysis demonstrated that reductions in pQCT values of the radius cortical bone were strongly predictive of vertebral and fragility peripheral fractures, but not pQCT trabecular vBMD and DXA aBMD [37].

Studies with HR-pQCT in non-CKD subjects have shown that alterations of cortical and trabecular structures

Table 3 Volumetric BMD, microstructural parameters, and cortical porosity in women and matched controls

		ESRD patients		Matched controls				Young controls
		Value	T-score	Value	T-score		% Difference (95 % CI)	Value
Radius	Dtot (mg/cm^3)	280±48***,**	−0.8±0.8	331±78	0.1±1.4	–	12 % (−24; −4)	327±57
	Dcort (mg/cm3)	859±90****	−0.7±1.9	928±58	0.7±1.2	–	7 % (−11; 1)	893±47
	C.Th (mm)	0.7±0.2*	−0.6±1.1	0.8±0.2	0.1±1.1	–	12 % (−24; 4)	0.8±0.2
	Dtrab (mg/cm^3)	120±41**	−1.1±1.1	148±34	−0.3±0.9	–	14 % (−39; 10)	160±37
	BV/TV (%)	10±3**	−0.9±1.1	12±3	−0.2±0.9	–	13 % (−36; 10)	13±3
	TbN (n/mm)	1.6±0.3***,**	−1.4±1.2	1.9±0.2	−0.3±1.0	–	12 % (−27; −3)	2.0±0.2
	TbTh (mm)	0.06±0.01**	−1.0±1.4	0.07±0.01	−0.5±1.1	–	5 % (−17; 16)	0.07±0.01
	TbSp (mm)	0.57±013***,**	1.7±1.8	0.47±0.06	0.3±0.9		24 % (2; 46)	0.44±0.07
	CSAtotal (mm^2)	242±33	−0.2±0.7	256±40	0.1±0.9	–	3 % (−17; 3)	252±44
	TbSp.SD	0.27±0.09***,**	2.4±2.3	0.20±0.04	0.6±1.1		43 % (5; 75)	0.18±0.04
	Cortical porosity (%)	2.9±3.9***	–	1.1±0.6	–		82 % (−6; 215)[a]	NA
	Cortical pore diameter (mm)	0.17±0.04	–	0.15±0.02	–		16 % (−7; 29)	NA
Tibia	Dtot (mg/cm^3)	238±36***,**	−1.6±0.7	280±54	−0.9±1.0	–	12 % (−30; 3)	328±55
	Dcort (mg/cm^3)	855±93****,**	−2.4±2.9	923±54	−0.3±1.7	–	7 %(−11; −1.1)	932±32
	CTh (mm)	0.9±0.2***,**	−1.3±1.1	1.1±0.2	−0.5±1.0	–	12 % (−27; −2)	1.2±0.2
	Dtrab (mg/cm3)	124±31***,**	−1.6±0.9	144±29	−1.1±0.8	–	11 % (−20; −8)	182±36
	BV/TV (%)	10±3***,**	−1.5±0.9	12±3	−1.0±0.8	–	10 % (−25; −8)	15±3
	TbN (n/mm)	1.6±0.3**	−0.9±1.0	1.7±0.3	−0.5±1.0	–	5 % (−20; 14)	1.9±0.3
	TbTh (mm)	0.07±0.01**	−1.3±1.2	0.07±0.01	−0.9±1.1	–	4 % (−25; 17)	0.08±0.01
	TbSp (mm)	0.59±0.12**	1.3±1.4	0.53±0.11	0.7±1.2		16 % (−10; 25)	0.47±0.09
	CSAtotal (mm^2)	662±102*	0.5±0.9	667±116	0.6±1.0		3 % (−14; 14)	604±113
	TbSp.SD	0.29±0.08**	2.2±2.1	0.25±0.08	1.3±1.9		24 % (−14; 61)	0.20±0.04
	Cortical porosity (%)	7.0±6.5	–	3.9±2.5	–		41 % (−8; 141)[a]	NA
	Cortical pore diameter (mm)	0.19±0.03	–	0.18±0.02	–		4 % (−5; 14)	NA

Values are means±SD. Total (Dtot), cortical (Dcort), and trabecular (Dtrab) volumetric density, expressed as milligram hydroxyapatite per cubic centimeter; trabecular bone volume fraction (BV/TV, in percent), trabecular number (TbN), trabecular thickness (TbTh, μm), trabecular separation (TbSp, in micrometer), heterogeneity of the trabecular network (TbSp.SD), cross-sectional area (CSAtotal, in square millimeter), and cortical thickness (CTh, in millimeter). Comparisons between ESRD patients and age-matched controls for continuous variables were performed with a Wilcoxon matched-pairs signed-ranks test. Comparisons between ESRD patients and young healthy controls were performed with a Kruskal–Wallis equality-of-populations rank test

$^{*}p<0.05$ as compared with gender-matched young healthy controls; $^{**}p<0.01$ as compared with gender-matched young healthy controls; $^{***}p<0.05$ as compared with age-, weight-, height-, and gender-matched controls; $^{****}p<0.01$ as compared with age-, weight-, and gender-matched controls

NA not assessed

[a] For the "% Difference" variable, given the skewness and large range of the percent difference of cortical porosity, the median was computed

are associated with fragility fractures, partially independent of decreased aBMD [13]. Similarly, vertebral fractures are associated with low vBMD and architectural decay of trabecular and cortical bone at the radius and tibia, independent of spine aBMD [38]. In CKD–MBD patients, HR-pQCT has been applied in predialysis chronic kidney disease patients >50 years [39]. In this study, patients with predialysis CKD and fractures had lower DXA-determined aBMD and lower vBMD, thinner cortices, and lower TbN than subjects without fractures. In another study, both aBMD and HR-pQCT parameters were associated with fractures among men and women with stages 3–5 CKD not on dialysis. The variable that discriminated between fractured and non-fractured patients was ultradistal radius aBMD. This variable was more predictive than any HR-pQCT parameter, and the addition of HR-pQCT results to ultradistal radius aBMD did not improve fracture discrimination [11]. In dialysis patients, Negri et al. [14] found a marked decrease in cortical density, thickness, and area, together with reductions in trabecular parameters in both men and women. However, these changes correlated with the severity of secondary hyperparathyroidism in women only. These findings are in

Table 4 Volumetric BMD, microstructural parameters, and cortical porosity in men and matched controls

		ESRD patients		Matched controls				Young controls
		Value	T-score	Value	T-score		% Difference (95 % CI)	
Radius	Dtot (mg/cm^3)	328±89	−0.7±1.5	346±58	−0.3±1.0	–	5 % (−22; 10)	366±58
	Dcort (mg/cm^3)	857±8****	−1.1±2.1	918±47	0.4±1.2	–	7 % (−10; −2)	902±40
	CTh (mm)	0.82±0.3	−0.6±1.7	0.96±0.2	0.2±1.2	–	14 % (−33; 10)	0.92±0.17
	Dtrab (mg/cm^3)	181±54	−0.5±1.4	162±24	−1.1±0.7		16 % (−12; 33)	202±37
	BV/TV (%)	15±5	−0.6±1.5	14±2	−1.1±0.7		14 % (−15; 30)	17±3
	TbN (n/mm)	2.1±0.3	−0.1±1.3	1.9±0.2	−0.9±1.1		11 % (−2; 23)	2.1±0.2
	TbTh (mm)	0.07±0.02*	−0.8±1.8	0.07±0.01	−0.9±1.4		5 % (−25; 45)	0.08±0.01
	TbSp (mm)	0.42±0.1	0.4±1.3	0.47±0.1	0.9±1.2	–	8 % (−19; −0.4)	0.40±0.06
	TbSp.SD	0.19±0.1	0.8±2.9	0.20±0.1	1.0±1.8		1 % (−24; 5)	0.17±0.03
	CSAtotal (mm^2)	354±71	0.3±1.2	340±62	0.1±1.0		6 % (−12; 24)	334±61
	Cortical porosity (%)	2.4±1.6	–	1.8±0.8	–		42 % (−16; 95)	NA
	Cortical pore diameter (mm)	0.16±0.03***	–	0.17±0.02	–	–	4 % (−13; −2)	NA
Tibia	Dtot (mg/cm^3)	277±60**	−1.2±0.9	308±53	−0.7±0.8	–	7 % (−25; 3)	362±54
	Dcort (mg/cm^3)	867±66*	−1.1±1.7	888±51	−0.6±1.3	–	2 % (−9; 4)	910±38
	C.Th (mm)	1.2±0.3*	−0.7±0.9	1.3±0.3	−0.3±0.8	–	8 % (31; 8)	1.4±0.3
	Dtrab (mg/cm^3)	149±50**	−1.5±1.1	179±34	−0.9±0.8	–	11 % (−28; 15)	218±45
	BV/TV (%)	14±3**	−1.1±0.9	15±3	−0.8±0.7	–	4 % (−28; 18)	18±4
	TbN (n/mm)	1.9±0.4*	−0.9±1.3	1.9±0.3	−0.8±1.1		2 % (−16; 13)	2.1±0.3
	TbTh (mm)	0.07±0.01**	−1.8±1.2	0.08±0.01	−1.0±1.1	–	8 % (−19; 0)	0.09±0.01
	TbSp (mm)	0.48±0.1*	1.5±2.1	0.46±0.1	1.2±1.8		10 % (−13; 23)	0.39±0.06
	TbSp.SD	0.25±0.1**	1.9±3.5	0.21±0.1	1.1±1.4		27 % (−20; 35)	0.17±0.04
	CSAtotal (mm^2)	865±142	0.3±0.9	865±154	0.3±1.0		2 % (−9; 3)	824±158
	Cortical porosity (%)	6.6±3.0	–	6.1±2.8	–		20 % (−28; 42)	NA
	Cortical pore diameter (mm)	0.19±0.02	–	0.19±0.02	–		1 % (−12; 11)	NA

Values are means ± SD. Total (Dtot), cortical (Dcort), and trabecular (Dtrab) volumetric density, expressed as milligram hydroxyapatite per cubic centimeter; trabecular bone volume fraction (BV/TV, in percent), trabecular number (TbN), trabecular thickness (TbTh, in micrometer), trabecular separation (TbSp, in micrometer), heterogeneity of the trabecular network (TbSp.SD), cross-sectional area (CSAtotal, in square millimeter), and cortical thickness (CTh, in millimeter). Comparisons between ESRD patients and matched controls for continuous variables were performed with a Wilcoxon matched-pairs signed-ranks test. Comparisons between ESRD patients and young healthy controls were performed with a Kruskal–Wallis equality-of-populations rank test

NA not assessed

$^{*}p<0.05$ as compared with gender-matched young healthy controls; $^{**}p<0.01$ as compared with gender-matched young healthy controls; $^{***}p<0.05$ as compared with age-, weight-, and gender-matched controls, $^{****}p<0.01$ as compared with age-, weight-, height-, and gender-matched controls

agreement with our results insofar as we observed also alterations in both cortical and trabecular compartments. The capacity of HR-pQCT to discriminate between patients with and without fractures in comparison to DXA in ESRD patients was also recently reported [15]. Whilst all these studies were cross-sectional, they often do not specify whether the fractures occurred during the dialysis period or previously. In our study, the number of fractures was very low and precluded any firm conclusion to be drawn regarding the potential of HR-pQCT results to predict fracture in ESRD patients.

Both cortical and trabecular compartments were affected and led to reduced bone strength, particularly in women, irrespective of the skeletal site assessed. There were some slight differences between distal radius and distal tibia, which may be related to the small number of subjects, hence to a limited power to detect significant differences. By integrating all microstructural variables, FEA-determined bone strength might be a more valid outcome to study the consequences of ESRD on bone than isolated variables. These results are similar to two recent publications [14, 15] and do not support the hypothesis of a selective cortical bone deficit in dialysis patients.

Male ESRD patients displayed only a lower radius cortical density. Indeed, they did not differ from age-matched healthy controls for most aBMD and microstructure variables.

Table 5 Summary of calculated bone strength (finite-element analysis parameters and polar moment of inertia) by gender and site

	Men		Women	
	Dialyzed (n=16)	Controls (n=16)	Dialyzed (n=17)	Controls (n=17)
Radius				
Stiffness (N mm)	102,135±21,943	108,046±14,918	60,791±12,553**	74,255±14,246
Predicted failure load (N)	4,872±1,009	5,130±700	2,881±602**	3,556±662
% Load trabecular bone distal	65±15*	56±13	58±15*	49±10
Apparent modulus	1,877±577	2,051±288	1,629±298*	1,841±466
Polar area moment of inertia (mm^4)	12,398±3,902	12,195±3,572	5,199±1,440*	7,534±4,731
Tibia				
Stiffness (N mm)	242,876±50,986	270,769±49,746	165,528±35,369**	190,374±22,462
Predicted failure load (N)	11,680±2,372	12,818±2,293	7,969±1,628**	9,131±1,038
% Load trabecular bone distal	58±10	58±9	54±17	50±10
Apparent modulus	2,155±493	2,358±423	1,932±346	2,195±184
Polar area moment of inertia (mm^4)	59,916±18,675	63,870±20,598	31,778±8,360	33,668±10,796

Values are mean ± SD

* $p<0.05$ as compared with age-, weight-, and gender-matched controls; ** $p<0.01$ as compared with age-, weight-, and gender-matched controls

However, we cannot provide a convincing explanation to account for the lack of differences between these two populations. It remains to be elucidated whether this may be due to the forces experienced by skeletal sites in men as the latter were approximately 18 kg heavier than the women [40], or whether men are less likely to restrain upper limb movement during scan acquisition. Indeed, measurement error with HR-pQCT at the radius is higher on average than that at the tibia [41].

As explanatory mechanisms of ESRD-associated microstructural defects, we found a negative correlation between cortical density and/or thickness and BALP, which emphasizes the role of bone turnover. Serum PTH is known to affect bone turnover and is used for the noninvasive assessment of bone turnover abnormalities in CKD-5D patients. Second-generation assays measure not only the intact PTH, but also several fragments, and it is well known that intact PTH measurement cannot reliably diagnose bone turnover, particularly when the range of serum PTH levels are within the range of KDIGO guidelines [16]. In our study, we had only few patients with very high PTH levels. However, one of the salient and original findings is the significant correlation between CtPo and KDIGO PTH level categories [42]. This observation is important since 80 % of our bone mass is cortical and 80 % of all fractures occur in non-vertebral sites that are mainly cortical. This change may be an important contributor of skeletal fragility as the cortical compartment supports a large majority of axial loads in the peripheral skeleton [27, 43]. Data from histomorphometric studies on CtPo in ESRD patients are scarce. In a study recently performed by Malluche et al. in black and white patients, it was shown that porosity was increased in 50 % of whites. When both black and white patients were analyzed together, CtPo was increased in patients with high bone turnover and with deeper erosion depth. Both BALP and serum PTH tended to be more elevated in patients with high CtPo, but not significantly [44]. In an experimental model of secondary hyperparathyroidism due to chronic renal failure in rats, an excess of CtPo was not apparent until serum PTH levels exceeded 500 pg/ml [45]. One hypothesis is that serum PTH excess may increase CtPo through an increase in bone turnover. To support this hypothesis, we observed a positive correlation between the percentage of load carried by the trabecular bone and BALP. Given the negative correlation between cortical density and/or thickness and BALP, this may reflect the negative impact of high bone turnover on the cortical compartment.

Protein-energy wasting is common in end-stage renal disease [46] and may affect 70–75 % of patients. Several factors contribute to these deficiencies, such as anorexia, increased protein catabolism, and reduced muscle synthesis, all of multifactorial origin. We observed a positive association between cortical density and nutritional status as assessed by MNA-SF, and to our knowledge, this is the first study to suggest that nutritional status may influence microstructural parameters in ESRD patients. We did not find, however, a correlation with protein intake "per se."

This study has several limitations. We studied a small number of ESRD patients, but patients were compared to well-matched controls and also to a young healthy population. We wanted to recruit a young population which has never been transplanted in order to capture the specific effect of end-stage renal disease on bone and not the effect of age or of corticosteroids. Unfortunately, recruitment goals

Table 6 Spearman's rank correlation coefficients of the association between bone microstructural parameters and demographic, dialysis, nutritional, and biological parameters

		R [*p* value]					
		Serum PTH[a]	BALP	BMI (kg/m^2)	MNA-SF	Protein intake (g/kg of body weight)	Dialysis duration (years)
aBMD	Lumbar spine BMD (g/cm^2)	−0.29 [0.10]	*−0.53 [0.01]*	*0.47 [0.01]*	*0.37 [0.04]*	−0.16 [0.37]	0.05 [0.79]
	Total hip BMD (g/cm^2)	−0.01 [0.98]	−0.32 [0.08]	*0.37 [0.03]*	*0.35 [0.05]*	0.10 [0.56]	0.23 [0.19]
Radius	Dtot (mg/cm^3)	0.09 [0.63]	−0.26 [0.16]	0.21 [0.24]	0.22 [0.23]	0.06 [0.72]	0.11 [0.55]
	Dcort (mg/cm^3)	0.03 [0.85]	*−0.36 [0.05]*	0.31 [0.08]	*0.42 [0.02]*	0.12 [0.52]	−0.16 [0.38]
	CTh (mm)	0.00 [0.99]	*−0.40 [0.03]*	0.32 [0.07]	0.30 [0.10]	0.09 [0.60]	0.06 [0.76]
	Dtrab (mg/cm^3)	0.11 [0.53]	−0.05 [0.81]	0.15 [0.40]	0.10 [0.57]	−0.05 [0.79]	0.18 [0.31]
	BV/TV (%)	0.12 [0.50]	−0.20 [0.94]	0.13 [0.47]	0.09 [0.61]	−0.06 [0.73]	0.18 [0.31]
	TbN (n/mm)	0.03 [0.86]	−0.19 [0.31]	0.27 [0.14]	0.21 [0.25]	−0.15 [0.40]	0.10 [0.57]
	TbTh (mm)	0.19 [0.30]	0.17 [0.37]	0.00 [1.00]	0.02 [0.93]	0.10 [0.59]	0.22 [0.22]
	TbSp (mm)	−0.05 [0.77]	0.15 [0.43]	−0.22 [0.22]	−0.22 [0.22]	0.12 [0.50]	−0.10 [0.56]
	CSAtotal (mm^2)	−0.19 [0.29]	−0.21 [0.26]	0.05 [0.78]	0.10 [0.60]	0.10 [0.58]	0.12 [0.49]
	TbSp.SD	−0.20 [0.90]	0.20 [0.29]	−0.26 [0.15]	−0.31 [0.08]	0.16 [0.38]	−0.15 [0.40]
	Cortical porosity (%)	0.20 [0.27]	0.13 [0.49]	0.06 [0.73]	−0.32 [0.07]	−0.13 [0.49]	0.18 [0.31]
	Stiffness (N mm)	0.05 [0.77]	−0.35 [0.06]	0.21 [0.24]	0.18 [0.32]	0.13 [0.46]	0.09 [0.61]
	Predicted failure load (N)	−0.03 [0.86]	−0.33 [0.07]	0.22 [0.22]	0.19 [0.29]	0.16 [0.39]	0.12 [0.50]
Tibia	Dtot (mg/cm^3)	0.09 [0.61]	−0.25 [0.18]	0.25 [0.16]	0.28 [0.12]	−0.06 [0.75]	0.08 [0.67]
	Dcort (mg/cm^3)	0.17 [0.34]	−0.34 [0.06]	0.10 [0.58]	*0.41 [0.02]*	0.14 [0.42]	−0.25 [0.16]
	CTh (mm)	0.06 [0.73]	*−0.37 [0.04]*	0.22 [0.22]	0.32 [0.07]	−0.01 [0.96]	−0.05 [0.78]
	Dtrab (mg/cm^3)	0.08 [0.64]	−0.00 [0.99]	0.10 [0.57]	−0.07 [0.71]	−0.14 [0.42]	0.11 [0.54]
	BV/TV (%)	0.01 [0.94]	−0.14 [0.46]	0.24 [0.18]	0.07 [0.71]	−0.15 [0.42]	0.10 [0.56]
	TbN (n/mm)	−0.08 [0.64]	−0.22 [0.23]	*0.40 [0.02]*	0.03 [0.87]	−0.28 [0.11]	0.10 [0.60]
	TbTh (mm)	0.12 [0.51]	0.11 [0.55]	−0.07 [0.70]	−0.02 [0.93]	0.09 [0.63]	−0.01 [0.95]
	TbSp (mm)	0.07 [0.70]	0.22 [0.23]	*−0.37 [0.03]*	−0.05 [0.79]	0.24 [0.18]	−0.11 [0.54]
	CSAtotal (mm^2)	−0.12 [0.50]	−0.28 [0.12]	0.19 [0.30]	0.09 [0.61]	0.10 [0.56]	0.02 [0.89]
	TbSp.SD	0.11 [0.54]	0.27 [0.14]	*−0.40 [0.02]*	−0.15 [0.41]	0.28 [0.11]	0.20 [0.26]
	Cortical porosity (%)	−0.08 [0.68]	0.20 [0.28]	0.01 [0.96]	−0.33 [0.06]	−0.06 [0.72]	0.29 [0.11]
	Stiffness (N mm)	−0.02 [0.93]	*−0.40 [0.03]*	*0.35 [0.04]*	0.28 [0.11]	−0.02 [0.92]	0.04 [0.83]
	Predicted failure load (N)	0.01 [0.95]	*−0.40 [0.03]*	*0.34 [0.05]*	0.27 [0.13]	−0.02 [0.93]	0.04 [0.84]

Significant coefficients of regression, beta (i.e., $p<0.05$) are italicized. The following variables, which are not significantly associated with any independent variables, are not included in the table: calcium intake and serum IGF1 level. Total (Dtot), cortical (Dcort), and trabecular (Dtrab) volumetric density, expressed as milligram hydroxyapatite per cubic centimeter; trabecular bone volume fraction (BV/TV, in percent), trabecular number (TbN), trabecular thickness (TbTh, in micrometer), trabecular separation (TbSp, in micrometer), heterogeneity of the trabecular network (TbSp.SD), cross-sectional area (CSAtotal, in square millimeter), and cortical thickness (CTh, in millimeter)

BALP Bone-specific alkaline phosphatase

[a] Based on a mean PTH value of two samples measured at 3-month intervals

were not met in time. One of the reasons is that a young population was rapidly referred for transplantation, and only older potential participants were available. Another reason was the unwillingness to be included in a clinical study. No power calculation was done, as the study was initially designed as exploratory. Thus, some differences have not been detected due to a possible lack of power. HR-pQCT provides an accurate evaluation of mineralized components, but it does not allow the evaluation of non-mineralized matrix. In addition, there were not enough patients with low-trauma fractures to find differences in HR-pQCT parameters between them and non-fractured controls. However, in addition to standard HR-pQCT morphologic outcomes, our study is strengthened by the assessment of CtPo, and bone strength and stiffness estimated from FEA. The studied patients were relatively young. Therefore, the results need to be interpreted in regard to a young ESRD population.

Conclusion

With the limitations due to a small number of patients studied, the results indicate that trabecular and cortical bone microstructure was altered in ESRD patients, as assessed by HR-pQCT. This was predominantly found in women. These changes translate into reduced bone strength and stiffness. The cortical compartment appears to be influenced by the level of bone turnover. Cortical porosity was related to category levels of parathyroid hormone.

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